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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171

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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT PAPER NUMBER

1632

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/558,149	NICOLAIDES, NICHOLAS	
	<b>Examiner</b>	<b>Art Unit</b>	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03/09/2006 and 05/08/2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 60-62, 71-75 and 81-96 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 60-62, 71-75 and 81-96 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 April 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

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### **DETAILED ACTION**

Applicant's replies dated 03/09/2006 and 05/08/2006 have been received. Claims 60-62,71,81-96 have been amended. Claims 60-62,71-75 and 81-96 are pending and under consideration in the instant office action.

#### ***Sequence Compliance***

Applicant's sequence submission dated 03/09/2006 is noted.

#### ***Specification***

The objection to the specification is withdrawn in light of Applicant's amendments to the specification.

#### ***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

#### ***New matter***

The rejection of claims 60-62 and 71-75 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and introducing new matter into the disclosure is withdrawn in light of Applicant's amendments to the claims. However, the amendments necessitate a new grounds of rejection as set forth below.

Claims 60-62 and 71 have been amended to recite "a dominant negative form of a PMS2 mismatch repair protein". Claim 81 limits the PMS2 gene of claim 62 to human PMS2. Claim 85

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limits the PMS2 gene of claim 61 to human PMS2. Claim 88 limits the PMS2 gene of claim 60 to human PMS2. Claim 91 limits the PMS2 gene of claim 71 to human PMS2.

The specification at page 7, lines 13-23 states that dominant negative alleles of a mismatch repair gene can be obtained from cells of humans, animals, yeast, bacteria or other organisms. However, the specification does not teach, generically, any dominant negative mutation of PMS2 other than truncation following amino acid 133 of human PMS2. The specification does not describe and mutations or truncations equivalent to truncation following amino acid 133 of human PMS2. Applicant has argued in response to the previous New Matter rejection of 11/09/2005, withdrawn above, that in the declaration of Dr. Nicolaides, submitted 11/05/2003, it is established that it was well within the skill of the ordinary skilled artisan to identify dominant negative forms of PMS as Arabidopsis PMS2-134 was shown to readily substitute for human PMS2-134. However, Applicant has failed to point out where the specification teaches truncation of the Arabidopsis PMS2 gene as discussed by the Nicolaides declaration submitted 11/05/2003. Thus, there is no support in the specification for any such substitution. In fact, the specification does not make specific reference to PMS2-134 or dominant negative PMS2 in any context other than referring to the known human PMS2-134 allele (see page 7, lines 4-9). The specification only refers to non-human alleles in the general context of dominant negative alleles of mismatch repair genes in general, not PMS2 specifically. There is no general description of the claimed genera of dominant negative PMS2 genes or alleles. There is no structural or functional correlation that would indicate what mutations other than truncation following amino acid 134 of human PMS2 that would lead to a dominant negative PMS2. The specification speculates why the PMS2-134 truncation is dominant negative as it appears to not

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interact with other MMR proteins, as originally hypothesized to be the means for causing a dominant negative effect. Applicant hypothesizes that the mechanism for the PMS2-134 effect is through inhibiting a downstream component of the MMR pathway as opposed to inhibiting the initial steps as originally expected (page 23, lines 7-22). Thus, it was not clear at the time of filing, how human PMS2-134 was acting as a dominant negative. While an understanding of how the disclosed invention operates is not essential, extrapolation of the disclosed species to the claimed breadth of dominant negative PMS2 mismatch repair genes requires a structural/functional correlation that would allow one of skill in the art to envision dominant negative mutations other than truncation following amino acid 133 of human PMS2.

Disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000).

#### *Enablement*

Claims 60-62, 71-75 and 81-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose germ and somatic cells all comprise a transgene encoding a dominant negative human PMS2-134 gene product wherein when the transgene is expressed the cells expressing the transgene exhibit hypermutability, does not reasonably provide enablement for the claimed mouse expressing any PMS2-134 gene or for the claimed mouse wherein the transgene is not expressed. The specification does not enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

To the extent that the specification has not described any other species of PMS2-134 gene that confers dominant negative activity (see rejections under 35 USC 112, 1<sup>st</sup> paragraph-New Matter and 35 USC 112, 2<sup>nd</sup> paragraph) the specification is not enabling for any species of PMS2-134 gene other human. The specification has prophetically taught making transgenic mice whose somatic and germ cells all comprise a transgene encoding a human PMS2-134 which is a mutant human gene comprising a truncation mutation at codon 134, resulting in a polypeptide with the N-terminal 133 amino acids. The specification has not taught that the PMS2 gene from a non-human species will have a dominant negative effect when truncated at amino acid 133. The specification does not teach or provide the means for determining that truncation of any PMS2 gene at amino acid 133 will result in proteins with the same function in mice. The specification does not provide PMS2 sequence from any other species to demonstrate any structural similarities in a way to allow determination of whether amino acid 133 from PMS2 of other species lies within the same functional domain.

Applicant argues, similar to that for the rejection under written description, that Applicants have provided substantial guidance in the specification for identifying polynucleotides comprising dominant negative forms of PMS2 mismatch repair genes along with indicators of the phenotype, enabling one of skill in the art to assess mutagenesis. Applicant refers again to the Nicolaides declaration establishing that other dominant negative forms of other mismatch repair genes were obtainable using the skill of the ordinary skilled artisan.

In response, Applicant has not provided any guidance with respect to any other dominant negative truncations of human PMS2 or any truncations or mutations of any other mismatch repair gene that would have the desired dominant negative effect. In fact, Applicant has only speculated as to why the truncation of human PMS2 at amino acid 134 leads to a dominant negative effect (see page 23, lines 7-22). Without an understanding of the mechanism of how such a truncation leads to dominant negative activity, it is not readily apparent to one of skill in the art how to manipulate other homologs and paralogs such that they will have dominant negative activity. There is no guidance in the specification as originally filed as to how to mutate any other PMS2 gene other than the human PMS2 gene described in the specification or how to mutate human PMS2 in any other way since the structural and functional correlation is not understood or taught by the specification. With respect to the declaration of Dr. Nicolaides, submitted 11/05/2003, Applicant demonstrates that truncation of Arabidopsis PMS2 at amino acid 134 is functionally equivalent to human PMS2-134. However, this is not sufficient to provide enablement for the full breadth of the claims encompassing any PMS2 gene including paralogs and homologs of human PMS2 that may vary in function following truncation at amino acid 134. Furthermore, Applicant has not presented any evidence for the existence of any dominant negative mutation other than human PMS2-134 and its equivalents from Arabidopsis to meet the breadth of the claims regarding other types of dominant negative mutations. In fact, the specification fails to mention Arabidopsis PMS2-134 at all.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 60-62, 71-75 and 81-96 under 35 U.S.C. 112, second paragraph is withdrawn in light of Applicant's amendments to the claims.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio  
Examiner  
Art Unit 1632



SCOTT D. PRIEBE, PH.D  
PRIMARY EXAMINER